A I D S TREATMENT N E W S

Issue Number 393
July 25, 2003

Published 18 times a year by
John S. James
AIDS Treatment News
1233 Locust St., 5th floor
Philadelphia, PA 19107

Contents

AIDS Treatment News

Subscription and Editorial Office:
AIDS Treatment News
Philadelphia FIGHT
1233 Locust St., 5th floor
Philadelphia, PA 19107
800-TREAT-1-2 toll-free U.S. and Canada
fax: 215-985-4952
email: aidsnews@aidsnews.org

Editor and Publisher: John S. James
Reader Services: Allison Dinsmore

Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

Subscription Information: Call 800-TREAT-1-2

Businesses, Institutions, Professional offices: $325/year. Includes early delivery of an extra copy by email.

Nonprofit community organizations: $150/year. Includes early delivery of an extra copy by email.

Individuals: $140/year, or $80 for six months.

Special discount for persons with financial difficulties: $54/year, or $30 for six months. If you cannot afford a subscription, please write or call.

Outside the U.S., Canada, or Mexico, add airmail postage of $20/year, or $10 for six months.

Back issues, and discounts for multiple subscriptions, are available; contact our office for details.

Please send U.S. funds: personal check or bank draft, international postal money order, or travelers checks. VISA, Mastercard, and purchase orders also accepted.

"If we discard the people who are dying from AIDS, then we can no longer call ourselves decent people."

Failure of Combination Abacavir + Tenofovir + Lamivudine (3TC)

In late July 2003 GlaxoSmithKline warned physicians that a three-drug combination of lamivudine (Epivir®), abacavir (Ziagen®) and tenofovir (Viread™) had failed to control HIV effectively in about half the treatment-naive patients in a clinical trial. The cause of the reduced response to this particular regimen is not known, but it may involve mutations causing cross-resistance to the drugs; Glaxo is also checking for chemical interactions inside the cell. The problem is not due to any one of the drugs; rather, for some reason this particular combination turned out not to work well.

The company advised:

"Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naive or pre-treated patients;

"Any patient currently controlled on therapy with this combination should be closely monitored and considered for modification of therapy; and

"Any usage of this triple

combination with other antiretroviral agents should be closely monitored for signs of treatment failure."

FTC (Emtriva™) Approved

by John S. James

The U.S. FDA announced the approval of FTC (brand name Emtriva, generic name emtricitabine, former brand name Coviracil™) on July 2, 2003.

FTC is chemically related to 3TC. It was approved primarily on the basis of two clinical trials: one comparing FTC with d4T, and the other comparing it with 3TC. FTC is taken once per day with or without food. Special dosing is needed for patients with kidney problems.

Shortly before approval, a clinical trial comparing FTC and d4T was stopped early by its Data Safety Monitoring Board (a somewhat unusual occurrence) because the patients in that trial who were randomly assigned to FTC were clearly doing better than those randomly assigned to d4T. (Note that all patients in this trial were also taking ddI [Videx®] and efavirenz [Sustiva®]; combining d4T and ddI is no longer recommended because of side effects, a problem that probably contributed to the superiority of FTC in this study.)

European approval is likely by late 2003.

FTC was approved mainly on the basis of two trials: the comparison with d4T above, and a trial in which patients who were on treatment including 3TC were randomly assigned to either stay on their current regimen or switch the 3TC to FTC. The patients in both groups did comparably well. Four percent of those on FTC discontinued it due to adverse events, vs. none who stayed on 3TC -- but this difference is hard to interpret since those who could not tolerate 3TC would have stopped that treatment earlier and could never have entered this particular trial.

FTC has had a long development history involving several companies, but now will be marketed worldwide by Gilead Sciences, Inc. (The drug has been shown to be active against HIV clades A, C, D, E, F, and G, --as well as against clade B, which causes almost all AIDS cases in the U.S.) In the U.S., Gilead announced that the "wholesaler acquisition cost" is $252.83 for a bottle of 30 capsules, a one-month supply.

The FDA's announcement noted that FTC has only been approved for adults age 18 and over, as pediatric safety and effectiveness have not been established. It suggested using resistance testing with pre-treated patients to check that their virus is likely to be susceptible to FTC (the

mutations M184V or M184I are the most common cause of viral resistance to FTC). It noted that about 1% of patients in clinical studies overall have discontinued FTC due to adverse events. It also recommended that all patients be tested for the presence of chronic hepatitis B virus before starting antiretroviral treatment for HIV, and that patients co-infected with hepatitis B be closely monitored for at least several months after FTC is discontinued, as there have been hepatitis B flare-ups when treatment is stopped. As with all members of this drug class (nucleoside reverse transcriptase inhibitors), the prescribing information carries a black-box warning about risk of lactic acidosis and liver toxicity.

The new HIV treatment guidelines (see article in this issue) did not consider FTC, because it was approved after the guidelines had been developed. FTC will be discussed in the next version.

Comment

As with any new drug, FTC's place in clinical practice will develop over time. This antiretroviral may have important advantages, but other treatments are much better known. Our guess is that many physicians will be conservative at first, but will use FTC as more is learned about long-term safety and effectiveness, and about which patients are most likely to benefit.

New HIV Treatment Guidelines Give More Advice

by John S. James

New HIV treatment guidelines for adults and adolescents, developed by a panel of experts convened by the U.S. Department of Human Services, were published July 14, 2003. This standard differs from previous editions in giving more direction to physicians, especially in choosing specific drugs. You can download this and other guidelines documents at http://AIDSinfo.nih.gov -- click Guidelines, then Adult and Adolescent Guidelines.

Advice on *when* to start antiretrovirals has not changed. But instead of the previous system (pick one drug from column A and two from column B), the new guidelines recommend choosing one of basically two preferred regimens, with alternates available if needed. There is also more guidance for doctors on how to deal with drug failure and choosing a new regimen.

Much of the useful information is contained in the 29 tables at the end of the 96-page document.

Comment

Guidelines are never the final word in a complicated, fast-changing, and controversial area of medicine. It is still critically important to have the advice of a physician with extensive experience in treating HIV.

HIV Drugs Approved as of August 2003

Here are all the antiretroviral drugs approved in the U.S. at the end of July 2003. We list them by drug class:

* NRTIs (nucleoside reverse transcriptase inhibitor) target reverse transcriptase (an enzyme of HIV), by providing false building blocks that the enzyme puts into new copies of the virus it is building. Occasionally the false building blocks can be incorporated into human DNA, causing toxicity.

* NNRTIs (non-nucleoside reverse transcriptase inhibitor) target the same reverse transcriptase enzyme, but do not provide false building blocks.

* Protease inhibitors target HIV protease, an enzyme necessary for late steps in the formation of new copies of HIV. Some protease inhibitors may inhibit certain human proteases as well, causing toxicity.

* Fusion inhibitors block infection early by preventing HIV from fusing with and entering a human cell. Only one fusion inhibitor has been approved so far, and this particular drug is expensive to manufacture and difficult to use.

None of these drugs can be taken alone to treat an established HIV infection. They must be used in well-designed combination regimens.

NRTIs:
Abacavir (Ziagen)
Didanosine - ddI (Videx)
Emtricitabine - FTC (Emtriva -- previous brand name Coviracil)
Lamivudine - 3TC (Epivir)
Stavudine - d4T (Zerit)
Tenofovir DF (Viread)
Zalcitabine - ddC (Hivid,)
Zidovudine - AZT (Retrovir)

NNRTIs
Delavirdine (Rescriptor)
Efavirenz (Sustiva, brand name Stocrin in many countries)
Nevirapine (Viramune)

Protease Inhibitors:
Amprenavir (Agenerase)
Atazanavir (Reyataz, formerly named Zrivada)
Indinavir (Crixivan)
Lopinavir+ritonavir (Kaletra)
Nelfinavir (Viracept)
Ritonavir (Norvir)
Saquinavir (Fortovase, earlier formulation Invirase)

Fusion Inhibitors
Enfuvirtide (Fuzeon)

Combination Medications

These brand names are combinations of two or three of the medicines above in one pill. Combinations reduce the number of pills patients must take each day. They can also help meet requirements of health plans that limit the number of "prescriptions" per month regardless of medical need.

Combivir (AZT + 3TC)
Trizivir (abacavir + AZT + 3TC)

Major HIV Treatment Conference in Paris -- Finding Reports Online

by John S. James

Here are some of the best Web sites for information about the 2nd IAS (International AIDS Society) Conference on HIV Pathogenesis and Treatment, July 13-16 in Paris. On these sites you can scan headlines and titles, then click on the articles you want to read. Keep in mind that new information from the Paris conference is being added all the time on these sites and elsewhere -- and that over the next several months much of the information from this conference will become less current, as newer findings are reported.

Notes:

(1) If a Web link in this article does not work, the site may have been reorganized. In that case go to the home page (usually the first part of the Web address, through the .com or .org) and look for the IAS (International AIDS Society) conference reports from there.

(2) It is best to read or skim through all the titles on the Web pages shown below. If there are many titles, a shortcut is to use the search (find) command in your browser. But this browser search will miss relevant articles if the titles do not happen to use the same words you specify.

Best Organized Site: Clinical Care Options, http://clinicaloptions.com/go/ias2003

This site, written primarily for medical professionals, may become the best Web presentation, and perhaps the most useful coverage of this conference overall.

Its IAS conference coverage is organized as seven tracks:

* Daily news
* First-line antiretroviral therapy
* Antiretroviral resistance & salvage therapy
* Clinical implications of studies of HIV pathogenesis
* Pharmacology & adverse effects of therapy
* Metabolic complications and lipodystrophy
* Opportunistic infections and coinfections

The daily news stories include protease inhibitors and cardiovascular disease, sex differences in fat redistribution (including noting that lipoatrophy is much more common in people with

HIV than had been expected), new T-20 information, high drug resistance in newly diagnosed people with HIV in Europe, and a number of reports on particular protease inhibitors and other antiretrovirals.

The other six sections include over 50 "capsule summaries" that present major clinical trials or other important conference presentations in a standardized table format. (For example, in the "Metabolic Complications and Lipodystrophy" track, the capsule summary on cardiovascular disease in a large cohort receiving antiretroviral therapy has outline-type presentations divided into these categories: Summary and key conclusions; Background; Summary of study design; Baseline characteristics of study population; and Main findings. Other capsule summaries can have different section titles, and narrative is allowed when needed.) This kind of presentation may seem strange at first, but we found it effective for presenting key information quickly. In August, Clinical Care Options expects to add analysis of the same information by three experts in each of the six areas covered in these tracks -- hopefully building on the capsule summaries, and providing more scrutiny and debate on the clinical implications than a single author's comments.

You need to register on the site to read the articles -- a free, one-time process that takes five to ten minutes. Most Web browsers can keep track of your user name and password, avoiding the need to log on every time you use the site.

Quick Summaries for Patients: The Body, http://www.thebody.com/confs/ias2003/complete.html

This page has titles and links to more than 50 short reports, divided into 25 topic areas (as of July 25, 2003). Readers can scan the titles, or search for a particular word in any of the titles, using the search function provided by most browsers. For example, we searched for "lipoatrophy" (which means fat wasting -- lipoatrophy can cause a sunken-face appearance, and often means that one's antiretroviral regimen needs to be changed). We found a topic area with five reports on lipoatrophy, and an additional report outside that topic area.

Some of the other topic areas involve:

* Drug resistance
* Antiretroviral therapy
* Complications of antiretroviral therapy
* Clinical trial results

While The Body is designed for patients, the IAS conference was held for medical professionals; some medical terms are unavoidable. If you want to search for a drug, the generic name is usually the best -- although you might want to try other names as well. For example, Fuzeon (the brand name of the drug also known as T-20) appears in a

title as the generic name, enfuvirtide. More importantly, be aware that different research can be confusing and contradictory, and some will be found to be wrong. Science is normally that way near the leading edge; only in schoolbooks are there usually clear lines between right and wrong ideas.

Reports for physicians: Medscape, http://www.medscape.com/viewprogram/2536

The Medscape HIV site reviews important late-breaker presentations (results too late to be submitted for regular consideration for the conference, but allowed in by a special procedure because of their value and timeliness). Late breaker session #1 includes the high rate of resistance found in Europe that was widely reported in the general press, the failure of week-on-week-off antiretroviral treatment, and the very important study showing that HIV transmission by breastfeeding could be prevented by treating the infant with either 3TC or nevirapine. Late breaker session #2 included a Canadian study on factors associated with resistance development (chiefly high viral load -- and intermediate adherence between 60% and 90%), good results from atazanavir in avoiding metabolic toxicities, and promising results from two new drugs active against many resistant viruses -- SPD754, a nucleoside analog, and TMC114, a protease inhibitor.

Outside the late breakers, some of the reports currently on the site include:

* Treatment access initiatives in developing countries;
* 48-week data for enfuvirtide (Fuzeon, T-20);
* Update on treatment interruption (15 abstracts were presented at the conference);
* Viral dynamics and fitness;
* Drug resistance update;
* New approaches to antiretroviral therapy;
* Complications of antiretroviral therapy;

Note: this site requires free registration. Also, early news reports now on the site may be replaced later by CME (continuing medical information) modules.

NATAP, http://www.natap.org/2003/IAS/ndxIAS.htm

The National AIDS Treatment Advocacy Project now has more than 15 articles, on subjects including antiretroviral regimens, drug resistance, hepatitis C treatment, human growth hormone, and methadone interactions.

HIVandHepatitis.com, http://www.hivandhepatitis.com/2003icr/2ndias/main.html

This site has over 40 articles on clinical trials, new experimental antiretrovirals, viral resistance, dosing, complications of antiretroviral therapy (over 15 articles), salvage therapy, pharmacology, drug supply, treatment interruption, preventing transmission, immuno